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Direct thrombin inhibitors in atrial fibrillation reloaded

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This editorial refers to ‘Oral direct thrombin inhibitor AZD0837 for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: a randomized dose-guiding, safety, and tolerability study of four doses of AZD0837 vs. vitamin K antagonists’[†], by G.Y.H. Lip *et al.* on page 2897

Inhibition of plasmatic coagulation is the key therapeutic principle for thromboprophylaxis and stroke prevention in atrial fibrillation. The coagulation cascade is initiated by contact of tissue factor (TF) with circulating factor (F) VIIa, resulting in the formation of the TF–VIIa complex. The latter catalyses the conversion of FIX to IXa and FX to Xa. Together with FVa, phospholipids, and calcium, FXa forms the ‘tenase’ or ‘prothrombinase’ complex, which catalyses the conversion of prothrombin (FII) to thrombin (FIIa), eventually resulting in fibrin formation and generation of a thrombus.¹ Thrombin furthermore activates FV, FVIII, and FXI by means of an auto-feedback loop, leading to the conversion of large amounts of FX to FXa and thereby to a sustained activation of coagulation (Figure 1).

For decades, vitamin K antagonists (VKAs), which prevent γ -carboxylation of vitamin-K dependent coagulation factors II, VII, IX, and X, have been the mainstay of therapy for stroke prevention in atrial fibrillation.² However, several downsides mainly related to their narrow therapeutic window are associated with long-term anticoagulation, necessitating life-long monitoring of coagulation intensity (initially 2–3 times weekly, later at least once monthly). Indeed, subtherapeutic as well as supratherapeutic anticoagulation with VKAs are associated with a substantial risk of recurrent events and bleeding (especially intracranial and gastrointestinal), respectively.

Not surprisingly, novel anticoagulants have been and are being developed for stroke prevention in atrial fibrillation in order to replace VKAs.³ In contrast to the latter, these new substances selectively inhibit central proteins of the coagulation cascade (Figure 1). Selective inhibitors of FXa and thrombin have turned out to be the most promising therapeutic principles in this regard. Direct thrombin inhibitors block the activity of thrombin

both in solution and in its fibrin-bound state, thereby impairing the conversion of fibrinogen to fibrin (Figure 1). Several years ago, the first oral direct thrombin inhibitor ximelagatran had demonstrated a similar efficacy to warfarin for stroke prevention in atrial fibrillation,⁴ when the drug had to be withdrawn from the market in February 2006 due to hepatotoxic side effects. Lip and colleagues have now reported on the findings of their phase II dose-finding study of the follow-up compound of ximelagatran, AZD0837, in patients with atrial fibrillation.⁵ In their trial, all four doses of AZD0837 were well tolerated, with similar rates of bleeding events compared with dose-adjusted VKAs. Although not designed to test clinical efficacy, all drug regimens had a similar effect on D-dimer levels (used as a biomarker of thrombogenesis). A dose of 300 mg once daily of AZD0837 was judged to provide the best safety and efficacy profile and will be taken to phase III.

In view of the experience with ximelagatran, patients with baseline serum alanine aminotransferase (ALT) >3-fold the upper limit of normal were excluded from the study. During the trial, the frequency of ALT elevation >3-fold normal was similar for AZD0837 and VKAs; this is in contrast to the phase II study with ximelagatran where a signal for liver enzyme elevations had been apparent.⁶ These data, together with the extensive data from studies with dabigatran etexilate, imply that severe liver toxicity does not appear to be a class effect of direct thrombin inhibitors but was rather a side effect observed specifically with ximelagatran. Nevertheless, some degree of ALT elevation was also observed with AZD0837, which normalized after cessation of the drug. It will hence be interesting and important to observe the development of liver function tests under AZD0837 meticulously during longer follow-up and in a larger cohort of patients.

Overall, the study of Lip *et al.*⁵ provides solid evidence of a favourable safety profile of the successor drug of ximelagatran, justifying further assessment of the drug in a phase III trial. Closer observation of the VKA comparator group, however, raises an important question. In general, both safety and efficacy of VKAs are critically dependent on the time patients are in the therapeutic international normalized ratio (INR) range (usually 2.0–3.0).⁷ In the present study, however, patients on VKAs were in the

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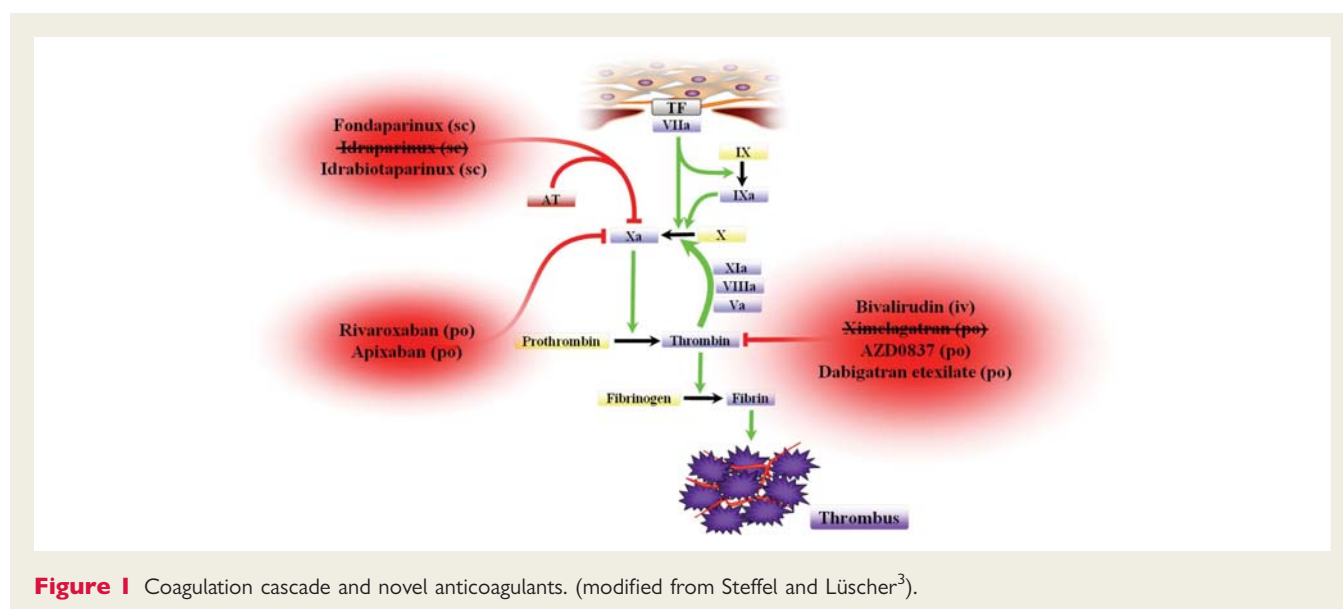


Figure 1 Coagulation cascade and novel anticoagulants. (modified from Steffel and Lüscher³).

therapeutic range only 58–68% of the time, which appears rather low, especially in the setting of a clinical trial. Indeed, subanalysis of the ACTIVE-W study has demonstrated that patients with atrial fibrillation who are in the therapeutic range during <65% of the time do not even derive a benefit from VKAs as compared with dual platelet inhibition with aspirin and clopidogrel,^{7,8} a treatment regimen otherwise inferior to VKA treatment in high risk patients.⁸ Achieving an optimal level of anticoagulation is a challenging task; although the time in the therapeutic range in the current study is similar to that observed in real life, it intuitively appears unsatisfactory for a clinical trial, in which optimal conditions should be the goal. Indeed, one could even argue that the comparator group may not represent a valid VKA control group if only insufficient levels of anticoagulation are achieved. As a consequence, conclusions with respect to efficacy and safety of the study drug would be difficult to interpret.

Several other novel anticoagulants have successfully undergone phase II studies and are currently being investigated in phase III trials. The ARISTOTLE study with apixaban (NCT00412984) is planned to finish recruitment by the end of 2010; the ROCKET-AF study with rivaroxaban (NCT00403767) is expected to be completed by mid 2010. Even earlier, results from the RE-LY study using the direct thrombin inhibitor dabigatran etexilate (NCT00262600) are expected to be presented at the forthcoming European Society of Cardiology meeting. While phase II studies unanimously look promising for these substances (including AZD0837), several issues with respect to their use currently remain unsolved. One of the most important aspects concerns the lack of need for monitoring in patients treated with these novel agents. Data from several phase III trials of rivaroxaban, dabigatran etexilate, and apixaban have demonstrated that this approach appears safe and effective for the prevention of venous thromboembolism after orthopaedic surgery. Although inhibition of platelet aggregation and specific inhibition of the coagulation cascade are not entirely comparable, the practical consequences of inadequate treatment due to the lack of monitoring parameters may be similar. Indeed, experience over the years has revealed that

clopidogrel, studied successfully using a fixed dose and without monitoring in clinical trials, may under 'real world' conditions be associated with a substantial degree of resistance (both genetic and acquired).^{9,10} As such, individual testing of its efficacy is increasingly being discussed, especially in view of the potentially devastating consequences of drug resistance.¹¹ A similar situation may be encountered with the novel anticoagulants. Pharmacokinetic as well as several phase II studies have implied that drug levels and treatment effects are independent of food intake and most concomitant medication; however, in the 'real world' setting of long-term treatment of patients with multiple co-morbidities, multiple medications, and intercurrent illnesses, application of these novel substances remains a 'black box' for the treating physician, with no established means of controlling treatment intensity. Since both lack of appropriate anticoagulation and overtreatment may lead to serious consequences, monitoring the degree of anticoagulation may turn out to be desirable for both efficacy and safety reasons. However, at present it is unclear in most cases which value [e.g. activated prothrombin time (aPTT), anti-FXa activity, INR, or drug level] should be assessed for monitoring which substance, and in which range target values would have to be expected. Ongoing (and planned) phase III studies may provide a great opportunity not only to investigate clinical endpoints, but also to assess comprehensively the validity, sensitivity, and specificity of monitoring parameters, to establish reference ranges, and to correlate these values with clinical outcomes.

All of this notwithstanding, data from the present study add to the growing evidence that VKAs will most probably be replaced by one or several novel anticoagulants for stroke prevention in atrial fibrillation. Nevertheless, previous lessons from ximelagatran have shown that only long-term application in large numbers of patients will conclusively reveal how AZD0837 (or, for that matter, any of the novel agents) compare with established VKAs regarding efficacy, safety, and adverse drug reactions. Whether or not monitoring of the anticoagulant effect of these substances will turn out to be important is going to be an interesting aspect.

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